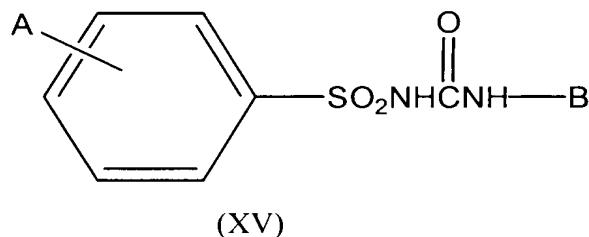


We Claim:

1. A pharmaceutical composition comprising a pharmaceutically effective amount of at least one insulin secretagogue and a pharmaceutically effective amount of at least one FBPase inhibitor.

2. The pharmaceutical composition of claim 1 wherein said insulin secretagogue is a sulfonylurea antidiabetic agent.

3. The pharmaceutical composition of claim 2 wherein said sulfonylurea antidiabetic agent is a compound of formula XV:



wherein

A is selected from hydrogen, halo, alkyl, alkanoyl, aryl, aralkyl, heteroaryl, and cycloalkyl; and

B is selected from alkyl, cycloalkyl, and heterocyclic alkyl.

4. The pharmaceutical composition of claim 2 wherein said sulfonylurea antidiabetic agent is selected from glyburide, glisoxepid, acetohexamide, chlorpropamide, glibornuride, tolbutamide, tolazamide, glipizide, gliclazide, gliquidone, glyhexamide, phenbutamide, tolcyclamide, and glimepiride.

5. The pharmaceutical composition of claim 1 wherein said insulin secretagogue is a non-sulfonylurea.

6. The pharmaceutical composition of claim 5 wherein said non-sulfonylurea is selected from mitiglinide, BTS-67582, repaglinide, and nateglinide.

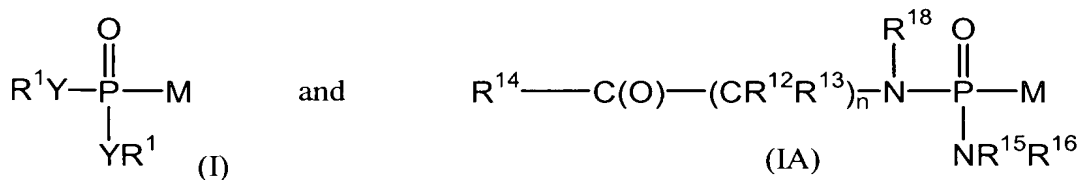
7. The pharmaceutical composition of claim 1 wherein said insulin
5 secretagogue is a dipeptidyl peptidase-IV (DPP-IV) inhibitor.

8. The pharmaceutical composition of claim 7 wherein said dipeptidyl peptidase-IV (DPP-IV) inhibitor is selected from the group of NVP-DPP728 and P32/98.

9. The pharmaceutical composition of claim 1 wherein said insulin
10 secretagogue is a glucagon like peptide-1 (GLP-1) receptor agonist.

10. The pharmaceutical composition of claim 9 where said glucagon like peptide-1 (GLP-1) receptor agonist is NN-2211, exendin, or an exendin agonist.

11. The pharmaceutical composition of claim 1 wherein said FBPase inhibitor is a compound selected from formulae I and IA and pharmaceutically acceptable prodrugs and salts thereof, wherein formulae I and IA are as follows:



20 wherein *in vivo* or *in vitro* compounds of formulae I and IA are converted to M-PO_3^{2-} , which inhibits FBPase, and wherein:

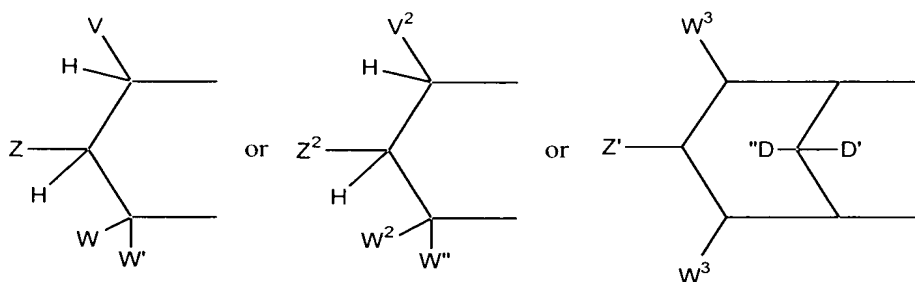
Y is independently selected from -O- and -NR⁶, with the provisos that:

when Y is -O-, the R¹ attached to -O- is independently selected from -H, alkyl, optionally substituted aryl, optionally substituted alicyclic where
25 the cyclic moiety contains a carbonate or a thiocarbonate, optionally substituted -arylalkyl, -C(R²)₂OC(O)NR²₂, -NR²-C(O)-R³, -C(R²)₂-OC(O)R³, -C(R²)₂-O-C(O)OR³, -C(R²)₂OC(O)SR³, -alkyl-S-C(O)R³, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy;

when Y is $-NR^6$ -, the R^1 attached to $-NR^6$ - is independently selected from $-H$ -, $-[C(R^2)_2]_q-COOR^3$ -, $-C(R^4)_2COOR^3$ -, $-[C(R^2)_2]_q-C(O)SR$ -, and $-cycloalkylene-COOR^3$ -, where q is 1 or 2;

when only one Y is $-O$ -, which $-O$ - is not part of a cyclic group containing the other Y, the other Y is $-N(R^{18})-(CR^{12}R^{13})-C(O)-R^{14}$; and

when Y is independently selected from $-O$ - and $-NR^6$ -, together R^1 and R^1 are alkyl-S-S-alkyl- and form a cyclic group, or together, R^1 and R^1 form :



wherein

a) V is selected from the group of aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkynyl and 1-alkenyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V; or

Z is selected from the group of $-CHR^2OH$ -, $-CHR^2OC(O)R^3$ -, $-CHR^2OC(S)R^3$ -, $-CHR^2OC(S)OR^3$ -, $-CHR^2OC(O)SR^3$ -, $-CHR^2OCO_2R^3$ -, $-OR^2$ -, $-SR^2$ -, $-CHR^2N_3$ -, $-CH_2aryl$ -, $-CH(aryl)OH$ -, $-CH(CH=CR^2_2)OH$ -, $-CH(C\equiv CR^2)OH$ -, $-R^2$ -, $-NR^2_2$ -, $-OCOR^3$ -, $-OCO_2R^3$ -, $-SCOR^3$ -, $-SCO_2R^3$ -, $-NHCOR^2$ -, $-NHCO_2R^3$ -, $-CH_2NHaryl$ -, $-(CH_2)_p-OR^2$ -, and $-(CH_2)_p-SR^2$ -, where p is an integer 2 or 3; or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

W and W' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl and 1-alkynyl; or

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

b) V^2 , W^2 and W'' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

Z^2 is selected from the group of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{SR}^2$, $-\text{CH}_2\text{NHaryl}$, $-\text{CH}_2\text{aryl}$; or

together V^2 and Z^2 are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally containing 1 heteroatom, and substituted with hydroxy, acyloxy, alkoxy, carbonyloxy, or aryloxy, carbonyloxy attached to a carbon atom that is three atoms from a Y attached to phosphorus;

c) Z' is selected from the group of $-\text{OH}$, $-\text{OC}(\text{O})\text{R}^3$, $-\text{OCO}_2\text{R}^3$, and $-\text{OC}(\text{O})\text{SR}^3$;

D' is -H;

D'' is selected from the group of -H, alkyl, $-\text{OR}^2$, $-\text{OH}$, and $-\text{OC}(\text{O})\text{R}^3$;

each W^3 is independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

with the proviso that:

a) V, Z, W, W' are not all -H and V^2 , Z^2 , W^2 , W'' are not all -H; and

R^2 is selected from R^3 and -H;

R^3 is selected from alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group of -H, alkylene, -alkylenearyl and aryl, or together R^4 and R^4 are connected via 2-6 atoms, optionally including one

5 heteroatom selected from the group of O, N, and S;

R^6 is selected from -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

n is an integer from 1 to 3;

R^{18} is independently selected from H, lower alkyl, aryl, and aralkyl, or, together,

10 R^{12} and R^{18} are connected via 1-4 carbon atoms to form a cyclic group;

each R^{12} and each R^{13} is independently selected from H, lower alkyl, lower aryl, lower aralkyl, all optionally substituted, or R^{12} and R^{13} , together, are connected via 2-6 carbon atoms, optionally including 1 heteroatom selected from the group of O, N, and S, to form a cyclic group;

15 each R^{14} is independently selected from $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, $-SR^{17}$, and $-NR^2R^{20}$;

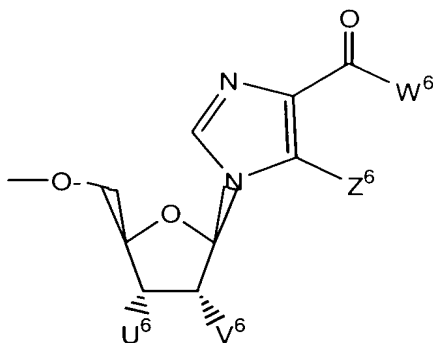
R^{15} is selected from -H, lower alkyl, lower aryl, and lower aralkyl, or, together, R^{15} and R^{16} are connected via 2-6 atoms to form a cyclic group, wherein the cyclic group optionally includes one heteroatom selected from O, N, and S;

20 R^{16} is selected from $-(CR^{12}R^{13})_n-C(O)-R^{14}$, -H, lower alkyl, lower aryl, and lower aralkyl, or, together, R^{15} and R^{16} are connected via 2-6 atoms to form a cyclic group, wherein the cyclic group optionally includes one heteroatom selected from O, N, and S;

each R^{17} is independently selected from lower alkyl, lower aryl, and lower aralkyl, or, when R^{14} is $-N(R^{17})_2$, together, both R^{17} s are connected via 2-6 atoms to form a cyclic group, wherein the cyclic group optionally includes one heteroatom selected from O, N, and S;

R^{20} is selected from the group of -H, lower R^3 , and $-C(O)$ -lower R^3 .

12. The pharmaceutical composition of claim 11 wherein M is:

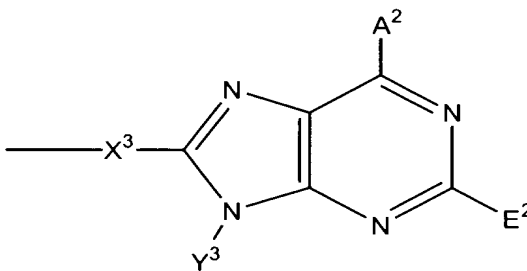


wherein:

- U⁶ and V⁶ are independently selected from hydrogen, hydroxy, and acyloxy, or, when taken together, U⁶ and V⁶ form a lower cyclic ring containing at least one oxygen;
W⁶ is selected from amino and lower alkyl amino; and
Z⁶ is selected from alkyl and halogen.

13. The pharmaceutical composition of claim 11 wherein said insulin secretagogue is a sulfonylurea antidiabetic agent.

14. The pharmaceutical composition of claim 11 wherein M is:



wherein:

- A² is selected from -NR⁸₂, -NHSO₂R³, -OR²⁵, -SR²⁵, halogen, lower alkyl, -CON(R⁴)₂, guanidine, amidine, -H, and perhaloalkyl;
E² is selected from -H, halogen, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and -NR⁷₂;

X^3 is selected from -alkyl(hydroxy)-; -alkyl-; -alkynyl-; -aryl-; -carbonyl-alkyl-; -1,1-dihaloalkyl-; -alkoxyalkyl-; -alkyloxy-; -alkylthioalkyl-; -alkylthio-; -alkylaminocarbonyl-; -alkylcarbonylamino-; -alicyclic-; -aralkyl-; -alkylaryl-; -alkoxycarbonyl-; -carbonyloxyalkyl-; -alkoxycarbonylamino-; and
5 -alkylaminocarbonylamino-, all optionally substituted, with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2$;

Y^3 is selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and
-OR³, all, except H, optionally substituted;

10 each R^4 is independently selected from -H and alkyl, or, together, both R^4 s form a cyclic alkyl group;

R^{25} is selected from lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

each R^7 is independently selected from -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

15 each R^8 is independently selected from -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or, together, both R^8 s form a bidendate alkyl;

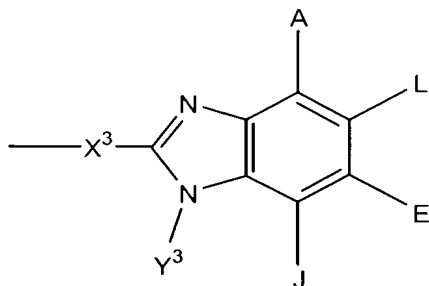
R^{10} is selected from -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from alkyl, aryl, $-NR^2_2$, and $-OR^2$;

and pharmaceutically acceptable prodrugs and salts thereof.

20 15. The pharmaceutical composition of claim 14 wherein said insulin secretagogue is a sulfonylurea antidiabetic agent.

16. The pharmaceutical composition of claim 11 wherein M is:



wherein:

A, E, and L are independently selected from $-NR^8_2$, $-NO_2$, $-H$, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^{25}$, $-SO_2NR^4_2$, $-CN$, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C_1 - C_5 alkyl, C_2 - C_5 alkenyl, C_2 - C_5 alkynyl, and lower alicyclic, or, together, A and L form a cyclic group, or, together, L and E form a cyclic group, or, together, E and J form a cyclic group selected from the group of aryl, cyclic alkyl, and heterocyclic;

J is selected from $-NR^8_2$, $-NO_2$, $-H$, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, $-CN$, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or, together, J and Y form a cyclic group selected from the group of aryl, cyclic alkyl, and heterocyclic alkyl;

X^3 is selected from -alkyl(hydroxy)-; -alkyl-; -alkynyl-; -aryl-; -carbonyl-alkyl-; -1,1-dihaloalkyl-; -alkoxyalkyl-; -alkyloxy-; -alkylthioalkyl-; -alkylthio-; -alkylaminocarbonyl-; -alkylcarbonylamino-; -alicyclic-; -aralkyl-; -alkylaryl-; -alkoxycarbonyl-; -carbonyloxyalkyl-; -alkoxycarbonylamino-; and -alkylaminocarbonylamino-, all optionally substituted, with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

Y^3 is selected from $-H$, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted;

each R^4 is independently selected from $-H$ and alkyl, or, together, both R^4 s form a cyclic alkyl group;

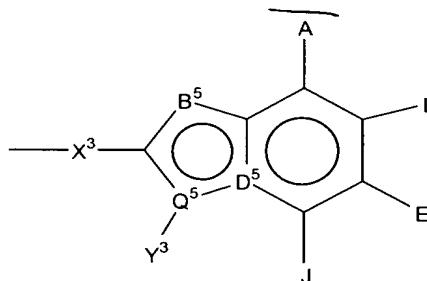
R^{25} is selected from lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;
each R^7 is independently selected from -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;
each R^8 is independently selected from -H, lower alkyl, lower aralkyl, lower aryl,
5 lower alicyclic, $-C(O)R^{10}$, or, together, both R^8 's form a bidendate alkyl;
 R^{10} is selected from -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl; and
 R^{11} is selected from alkyl, aryl, $-NR^2_2$, and $-OR^2$;
and pharmaceutically acceptable prodrugs and salts thereof.

10 17. The pharmaceutical composition of claim 16 wherein said insulin secretagogue is a sulfonylurea antidiabetic agent.

15 18. The pharmaceutical composition of claim 17 wherein said sulfonylurea antidiabetic agent is selected from glyburide, glisoxepid, acetohexamide, chlorpropamide, glibornuride, tolbutamide, tolazamide, glipizide, gliclazide, gliquidone, glyhexamide, phenbutamide, tolcyclamide, and glimepiride.

20 19. The pharmaceutical composition of claim 16 wherein said insulin secretagogue is selected from mitiglinide, BTS-67582, repaglinide, nateglinide, dipeptidyl peptidase-IV (DPP-IV) inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists.

20. The pharmaceutical composition of claim 11 wherein M is:



25 wherein:

B^5 is selected from $-NH-$, $-N=$ and $-CH=$;

D⁵ is selected from $\text{---}\overset{\textstyle |}{\text{C}}\text{=}$ and $\text{---}\overset{\textstyle |}{\text{N}}\text{---}$;

Q⁵ is selected from -C= and -N-;

with the provisos that:

when B⁵ is -NH-, Q⁵ is -C= and D⁵ is $\text{---}\overset{\textstyle |}{\text{C}}\text{=}$;

5 when B⁵ is -CH=, Q⁵ is -N- and D⁵ is $\text{---}\overset{\textstyle |}{\text{C}}\text{=}$; and

when B⁵ is -N=, D⁵ is $\text{---}\overset{\textstyle |}{\text{N}}\text{---}$ and Q⁵ is -C=;

A, E, and L are independently selected from -NR⁸₂, -NO₂, -H, -OR⁷, -SR⁷,
-C(O)NR⁴₂, halo, -COR¹¹, -SO₂R³, guanidine, amidine, -NHSO₂R²⁵, -SO₂NR⁴₂, -CN,
sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C₁-C₅ alkyl, C₂-C₅ alkenyl, C₂-C₅
10 alkynyl, and lower alicyclic, or, together, A and L form a cyclic group, or, together, L and
E form a cyclic group, or, together, E and J form a cyclic group selected from the group of
aryl, cyclic alkyl, and heterocyclic;

J is selected from -NR⁸₂, -NO₂, -H, -OR⁷, -SR⁷, -C(O)NR⁴₂, halo, -C(O)R¹¹,
-CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl,
15 aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic
group selected from the group of aryl, cyclic alkyl and heterocyclic alkyl;

X³ is selected from -alkyl(hydroxy)-, -alkyl-, -alkynyl-, -aryl-, -carbonyl-
alkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-,
-alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-,
20 -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and
-alkylaminocarbonylamino-, all optionally substituted; with the proviso that X³ is not
substituted with -COOR², -SO₃H, or -PO₃R²₂;

Y³ is selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl,
alkoxyalkyl, -C(O)R³, -S(O)₂R³, -C(O)-R¹¹, -CONHR³, -NR²₂, and -OR³, all except H are
25 optionally substituted;

R⁴ is independently selected from -H and alkyl, or together R⁴ and R⁴ form a
cyclic alkyl group;

R^{25} is selected from lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^7 is independently selected from -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidentate alkyl;

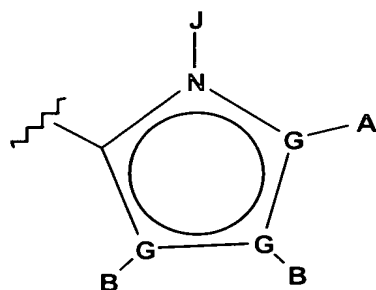
R^{10} is selected from -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from alkyl, aryl, $-NR^2_2$ and $-OR^3$;

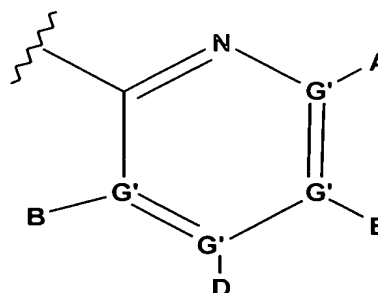
and pharmaceutically acceptable prodrugs and salts thereof.

21. The pharmaceutical composition of claim 20 wherein said insulin secretagogue is a sulfonylurea antidiabetic agent.

22. The pharmaceutical composition of claim 11 wherein M is $-X-R^5$ wherein R^5 is selected from:



and



wherein:

each G is independently selected from C, N, O, S, and Se, and wherein not more than one G is O, S, or Se, and not more than one G is N;

each G' is independently selected from C and N and wherein no more than two G' groups are N;

A is selected from -H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, perhaloalkyl, haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, $-CN$, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, $-NHAc$, and null;

each B and D are independently selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, -C(O)R¹¹, -C(O)SR³, -SO₂R¹¹, -S(O)R³, -CN, -NR⁹₂, -OR³, -SR³, perhaloalkyl, halo, -NO₂, and null, all except -H, -CN, perhaloalkyl, -NO₂, and halo are optionally substituted;

5 E is selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, alkoxyalkyl, -C(O)OR³, -CONR⁴₂, -CN, -NR⁹₂, -NO₂, -OR³, -SR³, perhaloalkyl, halo, and null, all except -H, -CN, perhaloalkyl, and halo are optionally substituted;

J is selected from -H and null;

10 X is an optionally substituted linking group that links R⁵ to the phosphorus atom via 2-4 atoms, including 0-1 heteroatoms selected from N, O, and S, except that if X is urea or carbamate there are 2 heteroatoms, measured by the shortest path between R⁵ and the phosphorus atom, and wherein the atom attached to the phosphorus is a carbon atom, and wherein X is selected from furan-2,5-diyl, -alkyl(hydroxy)-, -alkynyl-, -heteroaryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkyl-
15 thio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and -alkylaminocarbonylamino-, all optionally substituted; with the proviso that X is not substituted with -COOR², -SO₃H, or -PO₃R²₂;

R² is selected from R³ and -H;

R³ is selected from alkyl, aryl, alicyclic, and aralkyl;

20 each R⁴ is independently selected from -H, and alkyl, or together R⁴ and R⁴ form a cyclic alkyl group;

each R⁹ is independently selected from -H, alkyl, aralkyl, and alicyclic, or together R⁹ and R⁹ form a cyclic alkyl group or a heterocyclic group where the heteroatom is selected from the group of O, S and N;

25 R¹¹ is selected from alkyl, aryl, -NR²₂, and -OR²;

and with the proviso that:

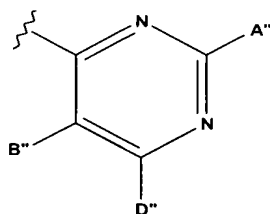
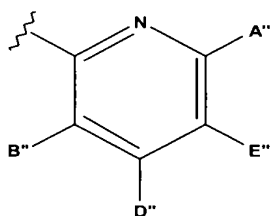
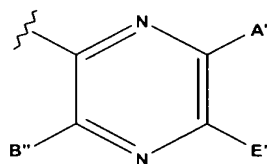
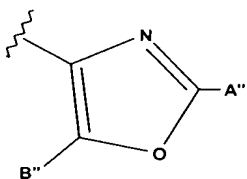
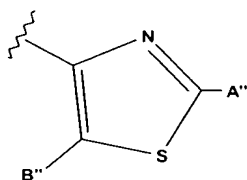
- 1) when G' is N, then the respective A, B, D, or E is null;
- 2) at least one of A and B, or A, B, D, and E is not selected from -H or null;
- 3) when R⁵ is a six-membered ring, then X is not any 2 atom linker, an
30 optionally substituted -alkyloxy-, or an optionally substituted -alkylthio-;

- 4) when G is N, then the respective A or B is not halogen or a group directly bonded to G via a heteroatom;
- 5) when X is not an -aryl- group, then R⁵ is not substituted with two or more aryl groups;
- 5 and pharmaceutically acceptable prodrugs and salts thereof.

23. The pharmaceutical compositions of claim 22 wherein R⁵ is selected from pyrrolyl; imidazolyl; oxazolyl; thiazolyl; isothiazolyl; 1,2,4-thiadiazolyl; pyrazolyl; isoxazolyl; 1,2,3-oxadiazolyl; 1,2,4-oxadiazolyl; 1,2,5-oxadiazolyl; 1,3,4-oxadiazolyl; 10 1,2,4-thiadiazolyl; 1,3,4-thiadiazolyl; pyridinyl; pyrimidinyl; pyrazinyl; pyridazinyl; 1,3,5-triazinyl; 1,2,4-triazinyl; and 1,3-selenazolyl, all of which contain at least one substituent.

24. The pharmaceutical composition of claim 22 wherein R⁵ is not 2-thiazolyl or 2-oxazolyl.

15 25. The pharmaceutical composition of claim 22 wherein R⁵ is selected from the group of:



wherein:

A'' is selected from -H, -NR⁴₂, -CONR⁴₂, -CO₂R³, halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perhaloalkyl, C₁-C₆ haloalkyl, aryl, -CH₂OH,

5 -CH₂NR⁴₂, -CH₂CN, -CN, -C(S)NH₂, -OR³, -SR³, -N₃, -NHC(S)NR⁴₂, and -NHAc;

B'' and D'' are independently selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, -C(O)R¹¹, -C(O)SR³, -SO₂R¹¹, -S(O)R³, -CN, -NR⁹₂, -OR³, -SR³, perhaloalkyl, and halo, all except -H, -CN, perhaloalkyl, and halo are optionally substituted;

10 E'' is selected from -H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₄-C₆ alicyclic, alkoxyalkyl, -C(O)OR³, -CONR⁴₂, -CN, -NR⁹₂, -OR³, -SR³, C₁-C₆ perhaloalkyl, and halo, all except H, -CN, perhaloalkyl, and halo are optionally substituted; and

each R^3 is independently selected from C_1 - C_6 alkyl, C_6 aryl, C_3 - C_6 heteroaryl, C_3 - C_8 alicyclic, C_2 - C_7 heteroalicyclic, C_7 - C_{10} aralkyl, and C_4 - C_9 heteroaralkyl;

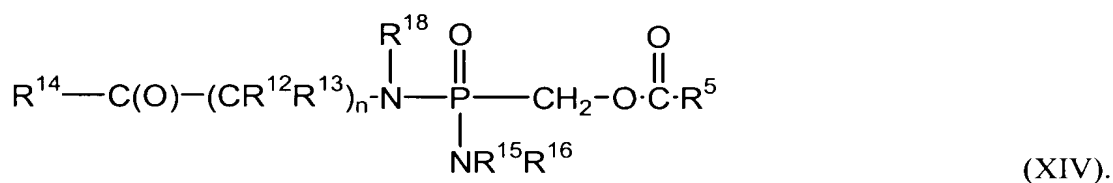
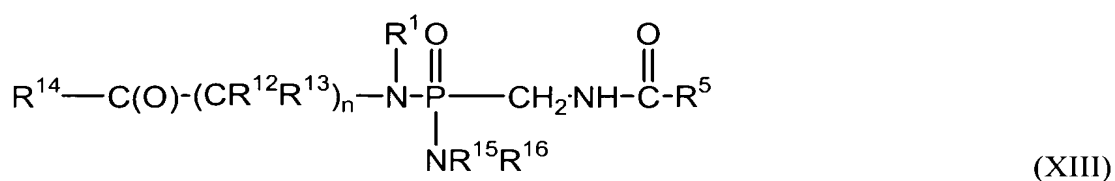
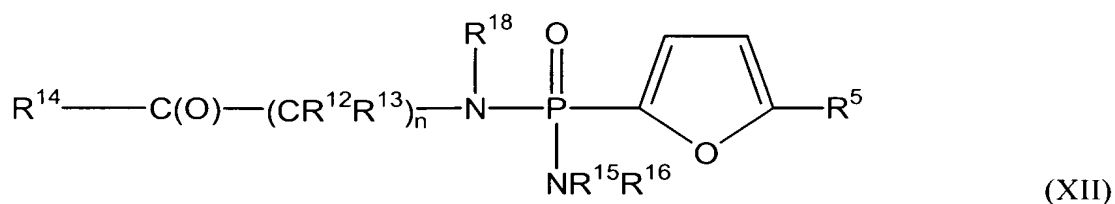
each R^4 and R^9 is independently selected from -H and C_1 - C_2 alkyl;

X is selected from -heteroaryl-, -alkylcarbonylamino-, -alkylaminocarbonyl-, and
5 -alkoxycarbonyl-;

each R^{11} is selected from $-NR^4_2$, -OH, $-OR^3$, C_1 - C_6 alkyl, C_6 aryl, and C_3 - C_6 heteroaryl.

26. The pharmaceutical composition of claim 25 wherein X is selected from
10 -heteroaryl- and -alkoxycarbonyl-.

27. The pharmaceutical composition of claim 25 wherein said compound is a
compound of formulae XII, XIII, or XIV:



28. The pharmaceutical composition of claim 25 wherein:
 A'' is selected from $-NH_2$, -Cl, -Br, and $-CH_3$;

each B'' is selected from -H, -C(O)OR³, -C(O)SR³, C1-C6 alkyl, alicyclic, halo, heteroaryl, and -SR³;

D'' is selected from -H, -C(O)OR³, lower alkyl, alicyclic, and halo; and

E'' is selected from -H, -Br, and -Cl.

5

29. The pharmaceutical composition of claim 27 wherein:

R¹⁸ is selected from -H, methyl, and ethyl;

each R¹² and R¹³ is independently selected from -H, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, -CH₂CH₂-SCH₃, phenyl, and benzyl, or together R¹² and R¹³ are connected via a chain of 2-5 carbon atoms to form a cycloalkyl group;

n is 1 or 2;

each R¹⁴ is independently selected from -OR¹⁷, wherein R¹⁷ is selected from methyl, ethyl, propyl, and benzyl; and

R¹⁵ and R¹⁶ are independently selected from lower alkyl and lower aralkyl, or together R¹⁵ and R¹⁶ are connected via a chain of 2-6 atoms, optionally including 1 heteroatom selected from O, N, and S.

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30. The pharmaceutical composition of claim 27 wherein R¹⁶ is -(CR¹²R¹³)_n-C(O)-R¹⁴.

20

31. The pharmaceutical composition of claim 27 wherein:

R¹⁸ is selected from -H, methyl, and ethyl;

R¹² and R¹³ are independently selected from -H, methyl, i-propyl, i-butyl, and benzyl, or together are connected via a chain of 2-5 carbon atoms to form a cycloalkyl group;

R¹⁴ is -OR¹⁷;

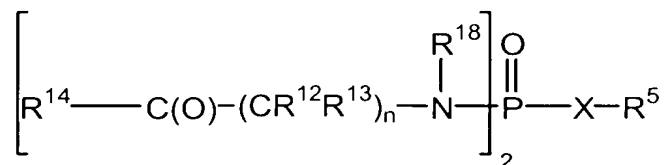
R¹⁷ is selected from methyl, ethyl, propyl, t-butyl, and benzyl; and

R¹⁵ and R¹⁶ are independently selected from lower alkyl, and lower aralkyl, or together R¹⁵ and R¹⁶ are connected via a chain of 2-6 atoms, optionally including 1 heteroatom selected from O, and N.

25

30

32. The pharmaceutical composition of claim 22 wherein said FBPase inhibitor is a compound of the formula:



wherein X is selected from furan-2,5-diyl; -alkoxycarbonyl-; and -alkylaminocarbonyl-.

33. The pharmaceutical composition of claim 32 wherein:

n is 1;

R¹² and R¹³ are independently selected from -H, methyl, i-propyl, i-butyl, and benzyl, or, together, R¹² and R¹³ are connected via a chain of 2-5 carbon atoms to form a cycloalkyl group, and, when R¹² and R¹³ are not the same,

H₂N-CR¹²R¹³-C(O)-R¹⁴ is an ester or thioester of a naturally occurring amino acid;

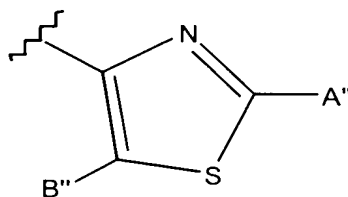
R¹⁴ is selected from -OR¹⁷ and -SR¹⁷;

R¹⁷ is selected from methyl, ethyl, propyl, t-butyl, and benzyl; and

R¹⁸ is selected from -H, methyl, and ethyl.

34. The pharmaceutical composition of claim 25 wherein:

R⁵ is:



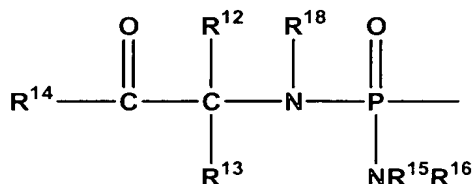
A'' is selected from -NH₂, -CONH₂, halo, -CH₃, -CF₃, -CH₂-halo, -CN, -OCH₃, -SCH₃, and -H;

B'' is selected from -H, -C(O)R¹¹, -C(OSR³), alkyl, aryl, alicyclic, halo, -CN, -SR³, OR³, and -NR⁹₂; and

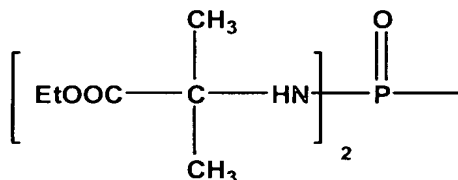
X is selected from -heteroaryl-, -alkoxycarbonyl-, and -alkylaminocarbonyl-,

all optionally substituted.

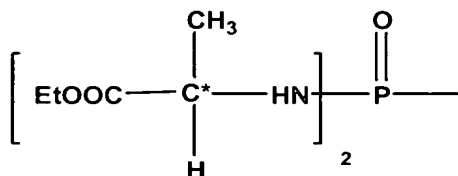
35. The pharmaceutical compositions of claim 34 wherein said FBPase inhibitor is a compound of Formula 1A and wherein:



is selected from



and



wherein:

C* has S stereochemistry;

R¹⁸ and R¹⁵ are independently selected from H and methyl;

each R¹² and R¹³ is independently selected from -H, methyl, i-propyl, i-butyl, and benzyl, or together R¹² and R¹³ are connected via a chain of 2-5 carbon atoms to form a cycloalkyl group;

n is 1;

R¹⁴ is -OR¹⁷;

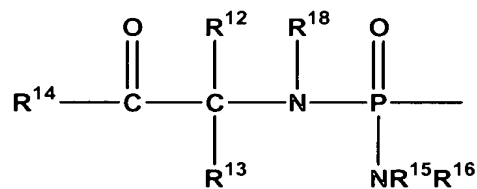
R¹⁶ is -(CR¹²R¹³)_n-C(O)-R¹⁴; and

R¹⁷ is selected from methyl, ethyl, propyl, phenyl, and benzyl.

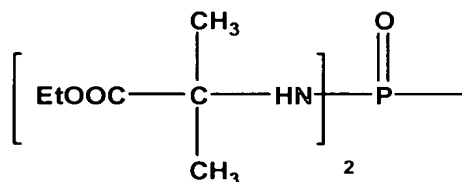
36. The pharmaceutical composition of claim 34 wherein A'' is -NH₂, X is furan-2,5-diyl, and B'' is -S(CH₂)₂CH₃.

37. The pharmaceutical composition of claim 34 wherein A'' is -NH₂, X is furan-2,5-diyl, and B'' is -CH₂-CH(CH₃)₂.

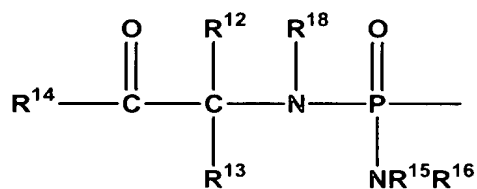
38. The pharmaceutical composition of claim 37 wherein said FBPase inhibitor is a compound of Formula 1A and wherein



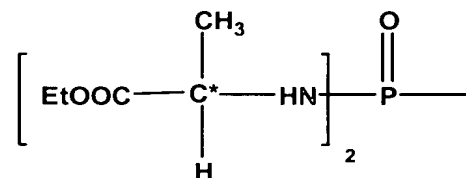
is



39. The pharmaceutical composition of claim 37 wherein said FBPase inhibitor is a compound of Formula 1A and wherein



is



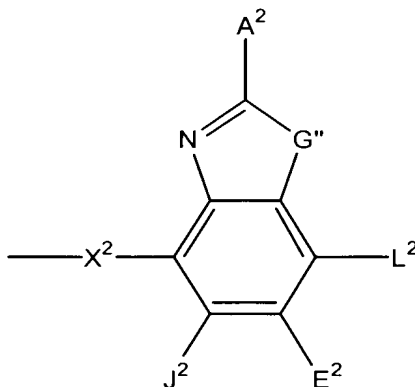
wherein C* has S stereochemistry.

40. The pharmaceutical composition of claim 22 wherein said insulin secretagogue is a sulfonylurea antidiabetic agent.

41. The pharmaceutical composition of claim 40 wherein said sulfonylurea antidiabetic agent is selected from glyburide, glisoxepid, acetohexamide, chlorpropamide, glibornuride, tolbutamide, tolazamide, glipizide, gliclazide, gliquidone, glyhexamide, phenbutamide, tolcyclamide, and glimepiride.

42. The pharmaceutical composition of claim 22 wherein said insulin secretagogue is selected from mitiglinide, BTS-67582, repaglinide, nateglinide, dipeptidyl peptidase-IV (DPP-IV) inhibitors, and glucagon like peptide-1 (GLP-1) receptor agonists.

43. The pharmaceutical composition of claim 11 wherein M is



wherein:

G'' is selected from -O- and -S-;

A², L², E², and J² are selected from -NR⁴, -NO₂, -H, -OR², -SR², -C(O)NR⁴, halo, -COR¹¹, -SO₂R³, guanidiny, amidiny, aryl, aralkyl, alkoxyalkyl, -SCN, -NHSO₂R⁹, -SO₂NR⁴, -CN, -S(O)R³, perhaloacyl, perhaloalkyl, perhaloalkoxy, C₁-C₅ alkyl, C₂-C₅ alkenyl, C₂-C₅ alkynyl, and lower alicyclic, or together L² and E² or E² and J² form an annulated cyclic group;

X^2 is selected from $-CR^2_2-$, $-CF_2-$, $-CR^2_2-O-$, $-CR^2_2-S-$, $-C(O)-O-$, $-C(O)-S-$, $-C(S)-O-$, and $-CR^2_2-NR^{19}-$, and wherein in the atom attached to the phosphorus is a carbon atom; with the proviso that X^2 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

5 R^2 is selected from R^3 and $-H$;

R^3 is selected from alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from $-H$, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

each R^9 is independently selected from $-H$, alkyl, aralkyl, and alicyclic, or together

10 R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from alkyl, aryl, $-NR^2_2$, and $-OR^2$;

R^{19} is selected from lower alkyl, $-H$, and $-COR^2$;

and pharmaceutically acceptable prodrugs and salts thereof.

15 44. The pharmaceutical composition of claim 43 wherein G'' is $-S-$.

45. The pharmaceutical composition of claim 43 wherein said insulin secretagogue is a sulfonylurea antidiabetic agent.

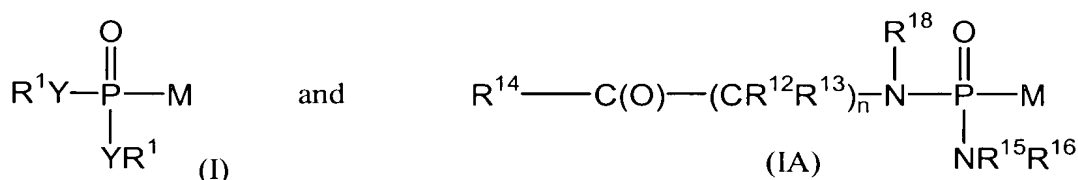
20 46. A method of treating a mammal having diabetes comprising administering to said mammal a pharmaceutically effective amount of a component (a) comprising at least one insulin secretagogue and a pharmaceutically effective amount of a component (b) comprising at least one FBPase inhibitor.

25 47. The method of claim 46 wherein said insulin secretagogue is a sulfonylurea antidiabetic agent.

48. The method of claim 47 wherein said sulfonylurea antidiabetic agent is selected from glyburide, glisoxepid, acetohexamide, chlorpropamide, glibornuride,
30 tolbutamide, tolazamide, glipizide, glyclazide, gliquidone, glyhexamide, phenbutamide, tolcyclamide, and glimepiride.

49. The method of claim 46 wherein said insulin secretagogue is selected from mitiglinide, BTS-67582, replaglinide, nateglinide, dipeptidyl peptidase-IV (DPP-IV) inhibitors, and glucagon like peptide-1 (GLP-1) receptor agonists.

50. The method of claim 46 wherein said FBPase inhibitor is a compound selected from formulae I and IA:



wherein *in vivo* or *in vitro* compounds of formulae I and IA are converted to M-PO_3^{2-} , which inhibits FBPase, and wherein:

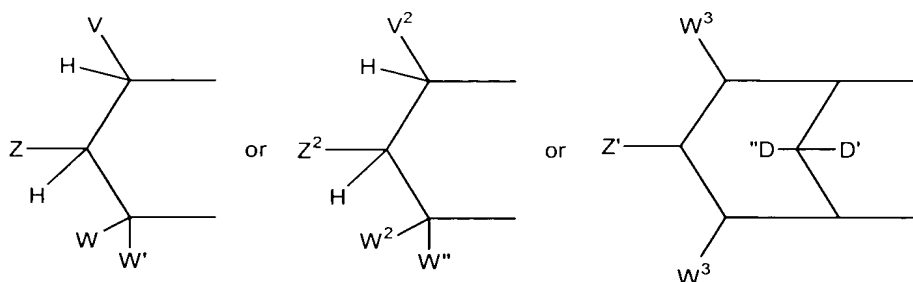
Y is independently selected from -O- and -NR⁶, with the provisos that:

when Y is -O-, the R¹ attached to -O- is independently selected from -H, alkyl, optionally substituted aryl, optionally substituted alicyclic where the cyclic moiety contains a carbonate or a thiocarbonate, optionally substituted -arylalkyl, -C(R²)₂OC(O)NR², -NR²-C(O)-R³, -C(R²)₂-OC(O)R³, -C(R²)₂-O-C(O)OR³, -C(R²)₂OC(O)SR³, -alkyl-S-C(O)R³, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy;

when Y is -NR⁶-, the R¹ attached to -NR⁶- is independently selected from -H, -[C(R²)₂]_q-COOR³, -C(R⁴)₂COOR³, -[C(R²)₂]_q-C(O)SR, and -cycloalkylene-COOR³, where q is 1 or 2;

when only one Y is -O-, which -O- is not part of a cyclic group containing the other Y, the other Y is -N(R¹⁸)-(CR¹²R¹³)-C(O)-R¹⁴;

when Y is independently selected from -O- and -NR⁶, together R¹ and R¹ are alkyl-S-S-alkyl- and form a cyclic group, or together, R¹ and R¹ form :



wherein

a) V is selected from the group of aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkynyl and 1-alkenyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V; or

Z is selected from the group of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2\text{aryl}$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$, $-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SCOR}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NHaryl}$, $-(\text{CH}_2)_p-\text{OR}^2$, and $-(\text{CH}_2)_p-\text{SR}^2$, where p is an integer 2 or 3; or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

W and W' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl and 1-alkynyl; or

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

b) V^2 , W^2 and W'' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

Z^2 is selected from the group of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{SR}^2$, $-\text{CH}_2\text{NHaryl}$, $-\text{CH}_2\text{aryl}$; or

together V^2 and Z^2 are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally containing 1 heteroatom, and substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxy carbonyloxy attached to a carbon atom that is three atoms from a Y attached to phosphorus;

c) Z' is selected from the group of $-\text{OH}$, $-\text{OC}(\text{O})\text{R}^3$, $-\text{OCO}_2\text{R}^3$, and $-\text{OC}(\text{O})\text{SR}^3$;

D' is $-\text{H}$;

D'' is selected from the group of $-\text{H}$, alkyl, $-\text{OR}^2$, $-\text{OH}$, and $-\text{OC}(\text{O})\text{R}^3$;

each W^3 is independently selected from the group of $-\text{H}$, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

with the proviso that:

a) V , Z , W , W' are not all $-\text{H}$ and V^2 , Z^2 , W^2 , W'' are not all $-\text{H}$;

R^2 is selected from R^3 and $-\text{H}$;

R^3 is selected from alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group of $-\text{H}$, alkylene, $-\text{alkylenearyl}$ and aryl, or together R^4 and R^4 are connected via 2-6 atoms, optionally including one heteroatom selected from the group of O, N, and S;

R^6 is selected from $-\text{H}$, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

n is an integer from 1 to 3;

R^{18} is independently selected from H, lower alkyl, aryl, and aralkyl, or, together, R^{12} and R^{18} are connected via 1-4 carbon atoms to form a cyclic group;

each R^{12} and each R^{13} is independently selected from H, lower alkyl, lower aryl,
5 lower aralkyl, all optionally substituted, or R^{12} and R^{13} , together, are connected via 2-6 carbon atoms, optionally including 1 heteroatom selected from the group of O, N, and S, to form a cyclic group;

each R^{14} is independently selected from $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, $-SR^{17}$, and $-NR^2R^{20}$;

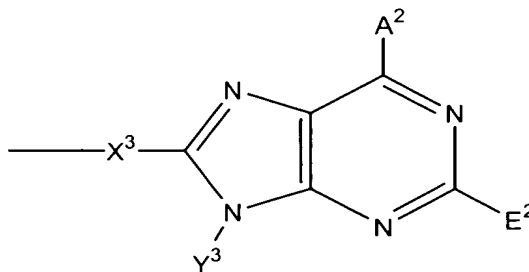
10 R^{15} is selected from -H, lower alkyl, lower aryl, and lower aralkyl, or, together, R^{15} and R^{16} are connected via 2-6 atoms to form a cyclic group, wherein the cyclic group optionally includes one heteroatom selected from O, N, and S;

R^{16} is selected from $-(CR^{12}R^{13})_n-C(O)-R^{14}$, -H, lower alkyl, lower aryl, and lower aralkyl, or, together, R^{15} and R^{16} are connected via 2-6 atoms to form a cyclic group,
15 wherein the cyclic group optionally includes one heteroatom selected from O, N, and S;

each R^{17} is independently selected from lower alkyl, lower aryl, and lower aralkyl, or, when R^{14} is $-N(R^{17})_2$, together, both R^{17} s are connected via 2-6 atoms to form a cyclic group, wherein the cyclic group optionally includes one heteroatom selected from O, N, and S;

20 R^{20} is selected from the group of -H, lower R^3 , and $-C(O)$ -lower R^3 ;
and pharmaceutically acceptable prodrugs and salts thereof.

51. The method of claim 50 wherein M is:



wherein:

A^2 is selected from $-NR^8_2$, $NHSO_2R^3$, $-OR^{25}$, $-SR^{25}$, halogen, lower alkyl, $-CON(R^4)_2$, guanidine, amidine, -H, and perhaloalkyl;

E^2 is selected from -H, halogen, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7_2$;

5 X^3 is selected from -alkyl(hydroxy)-, -alkyl-, -alkynyl-, -aryl-, -carbonyl-alkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and -alkylaminocarbonylamino-, all optionally substituted; with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

10 Y^3 is selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted;

15 each R^4 is independently selected from -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^{25} is selected from lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^7 is independently selected from -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

20 R^8 is independently selected from -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^{10} is selected from -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from alkyl, aryl, $-NR^2_2$, and $-OR^2$, and

pharmaceutically acceptable prodrugs and salts thereof.

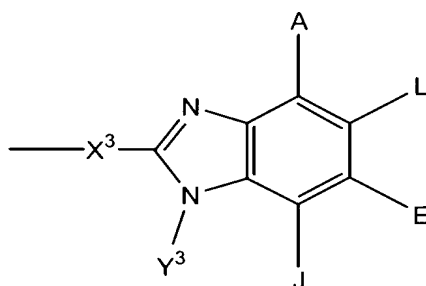
25 52. The method of claim 51 wherein said insulin secretagogue is a sulfonylurea antidiabetic agent.

53. The method of claim 52 wherein said sulfonylurea antidiabetic agent is selected from glyburide, glisoxepid, acetohexamide, chlorpropamide, glibornuride,

tolbutamide, tolazamide, glipizide, gliclazide, gliquidone, glyhexamide, phenbutamide, tolcyclamide, and glimepiride.

54. The method of claim 51 wherein said insulin secretagogue is selected from mitiglinide, BTS-67582, repaglinide, nateglinide, dipeptidyl peptidase-IV (DPP-IV) inhibitors, and glucagon like peptide-1 (GLP-1) receptor agonists.

55. The method of claim 50 wherein M is:



wherein:

A, E, and L are selected from $-NR^8_2$, $-NO_2$, $-H$, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^{25}$, $-SO_2NR^4_2$, $-CN$, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group selected from the group of aryl, cyclic alkyl, and heterocyclic;

J is selected from $-NR^8_2$, $-NO_2$, $-H$, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, $-CN$, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group selected from the group of aryl, cyclic alkyl and heterocyclic alkyl;

X^3 is selected from $-alkyl(hydroxy)-$, $-alkyl-$, $-alkynyl-$, $-aryl-$, $-carbonyl-alkyl-$, $-1,1-dihaloalkyl-$, $-alkoxyalkyl-$, $-alkyloxy-$, $-alkylthioalkyl-$, $-alkylthio-$, $-alkylaminocarbonyl-$, $-alkylcarbonylamino-$, $-alicyclic-$, $-aralkyl-$, $-alkylaryl-$,

-alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and
-alkylaminocarbonylamino-, all optionally substituted; with the proviso that X^3 is not
substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2$;

Y^3 is selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl,
5 alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are
optionally substituted;

each R^4 is independently selected from -H, and alkyl, or together R^4 and R^4 form a
cyclic alkyl group;

R^{25} is selected from lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

10 R^7 is independently selected from -H, lower alkyl, lower alicyclic, lower aralkyl,
lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from -H, lower alkyl, lower aralkyl, lower aryl, lower
alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^{10} is selected from -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

15 R^{11} is selected from alkyl, aryl, $-NR^2_2$, and $-OR^2$;

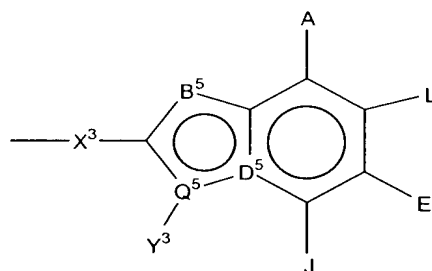
and pharmaceutically acceptable prodrugs and salts thereof.

56. The method of claim 55 wherein said secretagogue is a sulfonylurea
antidiabetic agent.

20 57. The method of claim 56 wherein said sulfonylurea antidiabetic agent is
selected from glyburide, glisoxepid, acetohexamide, chlorpropamide, glibornuride,
tolbutamide, tolazamide, glipizide, gliclazide, gliquidone, glyhexamide, phenbutamide,
tolcyclamide, and glimepiride.

25 58. The method of claim 55 wherein said insulin secretagogue is selected from
mitiglinide, BTS-67582, repaglinide, nateglinide, dipeptidyl peptidase-IV (DPP-IV)
inhibitors, and glucagon like peptide-1 (GLP-1) receptor agonists.

30 59. The method of claim 50 wherein M is:



wherein:

B^5 is selected from $-NH-$, $-N=$ and $-CH=$;

D^5 is selected from $\begin{array}{c} | \\ -C= \end{array}$ and $\begin{array}{c} | \\ -N- \end{array}$;

Q^5 is selected from $-C=$ and $-N-$;

with the provisos that:

when B^5 is $-NH-$, Q^5 is $-C=$ and D^5 is $\begin{array}{c} | \\ -C= \end{array}$;

when B^5 is $-CH=$, Q^5 is $-N-$ and D^5 is $\begin{array}{c} | \\ -C= \end{array}$; and

when B^5 is $-N=$, then D^5 is $\begin{array}{c} | \\ -N- \end{array}$ and Q^5 is $-C=$;

A, E, and L are selected from $-NR^8_2$, $-NO_2$, $-H$, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^{25}$, $-SO_2NR^4_2$, $-CN$, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group selected from the group of aryl, cyclic alkyl, and heterocyclic;

J is selected from $-NR^8_2$, $-NO_2$, $-H$, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, $-CN$, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group selected from the group of aryl, cyclic alkyl and heterocyclic alkyl;

X^3 is selected from $-alkyl(hydroxy)-$, $-alkyl-$, $-alkynyl-$, $-aryl-$, $-carbonyl-$, $-alkyl-$, $-1,1-dihaloalkyl-$, $-alkoxyalkyl-$, $-alkyloxy-$, $-alkylthioalkyl-$, $-alkylthio-$, $-alkylaminocarbonyl-$, $-alkylcarbonylamino-$, $-alicyclic-$, $-aralkyl-$, $-alkylaryl-$,

-alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and
-alkylaminocarbonylamino-, all optionally substituted; with the proviso that X^3 is not
substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2$;

Y^3 is selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl,
5 alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are
optionally substituted;

each R^4 is independently selected from -H and alkyl, or together R^4 and R^4 form a
cyclic alkyl group;

R^{25} is selected from lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

10 R^7 is independently selected from -H, lower alkyl, lower alicyclic, lower aralkyl,
lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from -H, lower alkyl, lower aralkyl, lower aryl, lower
alicyclic, $-C(O)R^{10}$, or together they form a bidentate alkyl;

R^{10} is selected from -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

15 R^{11} is selected from alkyl, aryl, $-NR^2_2$ and $-OR^2$; and
pharmaceutically acceptable prodrugs and salts thereof.

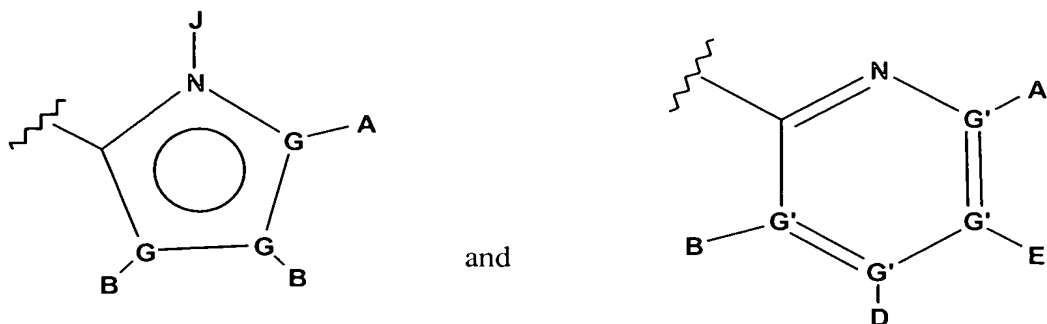
60. The method of claim 59 wherein said insulin secretagogue is a sulfonylurea
antidiabetic agent.

20 61. The method of claim 60 wherein said sulfonylurea antidiabetic agent is
selected from glyburide, glisoxepid, acetohexamide, chlorpropamide, glibornuride,
tolbutamide, tolazamide, glipizide, gliclazide, gliquidone, glyhexamide, phenbutamide,
tolcyclamide, and glimepiride.

25 62. The method of claim 59 wherein said insulin secretagogue is selected from
mitiglinide, BTS-67582, replaglinide, nateglinide, dipeptidyl peptidase-IV (DPP-IV)
inhibitors, and glucagon like peptide-1 (GLP-1) receptor agonists.

30 63. The method of claim 50 wherein M is $-X-R^5$ wherein

R^5 is selected from:



wherein:

each G is independently selected from C, N, O, S, and Se, and wherein not more than one G is O, S, or Se, and not more than one G is N;

each G' is independently selected from C and N and wherein no more than two G' groups are N;

A is selected from -H, -NR⁴₂, -CONR⁴₂, -CO₂R³, halo, -S(O)R³, -SO₂R³, alkyl, alkenyl, alkynyl, perhaloalkyl, haloalkyl, aryl, -CH₂OH, -CH₂NR⁴₂, -CH₂CN, -CN, -C(S)NH₂, -OR³, -SR³, -N₃, -NHC(S)NR⁴₂, -NHAc, and null;

each B and D are independently selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, -C(O)R¹¹, -C(O)SR³, -SO₂R¹¹, -S(O)R³, -CN, -NR⁹₂, -OR³, -SR³, perhaloalkyl, halo, -NO₂, and null, all except -H, -CN, perhaloalkyl, -NO₂, and halo are optionally substituted;

E is selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, alkoxyalkyl, -C(O)OR³, -CONR⁴₂, -CN, -NR⁹₂, -NO₂, -OR³, -SR³, perhaloalkyl, halo, and null, all except -H, -CN, perhaloalkyl, and halo are optionally substituted;

J is selected from -H and null;

X is an optionally substituted linking group that links R⁵ to the phosphorus atom via 2-4 atoms, including 0-1 heteroatoms selected from N, O, and S, except that if X is urea or carbamate, then there are 2 heteroatoms, measured by the shortest path between R⁵ and the phosphorus atom, and wherein the atom attached to the phosphorus is a carbon atom, and wherein X is selected from -alkyl(hydroxy)-, -alkynyl-, -heteroaryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-,

-alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-,
-alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and
-alkylaminocarbonylamino-, all optionally substituted; with the proviso that X is not
substituted with $-\text{COOR}^2$, $-\text{SO}_3\text{H}$, or $-\text{PO}_3\text{R}^2_2$;

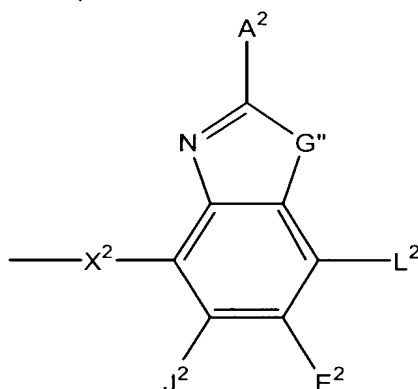
- 5 R^2 is selected from R^3 and $-\text{H}$;
 R^3 is selected from alkyl, aryl, alicyclic, and aralkyl;
each R^4 is independently selected from $-\text{H}$, and alkyl, or together R^4 and R^4 form a
cyclic alkyl group;
each R^9 is independently selected from $-\text{H}$, alkyl, aralkyl, and alicyclic, or together
10 R^9 and R^9 form a cyclic alkyl group;
 R^{11} is selected from alkyl, aryl, $-\text{NR}^2_2$, and $-\text{OR}^2$;
and with the proviso that:
- 1) when G' is N, then the respective A, B, D, or E is null;
 - 2) at least one of A and B, or A, B, D, and E is not selected from $-\text{H}$ or null;
 - 15 3) when R^5 is a six-membered ring, then X is not a two atom linker, an
optionally substituted -alkyloxy-, or an optionally substituted -alkylthio-;
 - 4) when G is N, then the respective A or B is not halogen or a group directly
bonded to G via a heteroatom;
 - 5) when X is not an -aryl- group, then R^5 is not substituted with two or more
20 aryl groups;
and pharmaceutically acceptable prodrugs and salts thereof.

64. The method of claim 63 wherein said insulin secretagogue is a sulfonylurea
antidiabetic agent.

25 65. The method of claim 64 wherein said sulfonylurea antidiabetic agent is
selected from glyburide, glisoxepid, acetohexamide, chlorpropamide, glibornuride,
tolbutamide, tolazamide, glipizide, gliclazide, gliquidone, glyhexamide, phenbutamide,
tolcyclamide, and glimepiride.

66. The method of claim 63 wherein said secretagogue is selected from mitiglinide, BTS-67582, replaglinide, nateglinide, dipeptidyl peptidase IV (DPP-IV) inhibitors, and glucagon like peptide-1 (GLP-1) receptor agonists.

5 67. The method of claim 50 wherein M is:



wherein:

G'' is selected from -O- and -S-;

10 A², L², E², and J² are selected from -NR⁴₂, -NO₂, -H, -OR², -SR², -C(O)NR⁴₂, halo, -COR¹¹, -SO₂R³, guanidiny, amidiny, aryl, aralkyl, alkoxyalkyl, -SCN, -NHSO₂R⁹, -SO₂NR⁴₂, -CN, -S(O)R³, perhaloacyl, perhaloalkyl, perhaloalkoxy, C₁-C₅ alkyl, C₂-C₅ alkenyl, C₂-C₅ alkynyl, and lower alicyclic, or together L² and E² or E² and J² form an annulated cyclic group;

15 X² is selected from -CR²₂-, -CF₂-, -CR²₂-O-, -CR²₂-S-, -C(O)-O-, -C(O)-S-, -C(S)-O-, and -CR²₂-NR¹⁹-, and wherein in the atom attached to the phosphorus is a carbon atom; with the proviso that X² is not substituted with -COOR², -SO₃H, or -PO₃R²₂;

R² is selected from R³ and -H;

20 R³ is selected from alkyl, aryl, alicyclic, and aralkyl;

each R⁴ is independently selected from -H, and alkyl, or together R⁴ and R⁴ form a cyclic alkyl group;

each R⁹ is independently selected from -H, alkyl, aralkyl, and alicyclic, or together R⁹ and R⁹ form a cyclic alkyl group;

R¹¹ is selected from alkyl, aryl, -NR²₂, and -OR²;

R¹⁹ is selected from lower alkyl, -H, and -COR²;

5 and pharmaceutically acceptable salts or prodrugs thereof.

68. The method of claim 67 wherein said insulin secretagogue is a sulfonylurea antidiabetic agent.

10 69. The method of claim 68 wherein said sulfonylurea antidiabetic agent is selected from glyburide, glisoxepid, acetohexamide, chlorpropamide, glibornuride, tolbutamide, tolazamide, glipizide, gliclazide, gliquidone, glyhexamide, phenbutamide, tolcyclamide, and glimepiride.

15 70. The method of claim 67 wherein said insulin secretagogue is selected from mitiglinide, BTS-67582, replaglinide, nateglinide, dipeptidyl peptidase-IV (DPP-IV) inhibitors, and glucagon like peptide-1 (GLP-1) receptor agonists.

20 71. The method of claim 46 wherein said combination is administered orally.

72. The method of claim 46 wherein said disease is characterized by hyperglycemia.

73. The method of claim 46 wherein said disease is obesity.

25 74. The method of claim 46 wherein from about 100 mg to about 2,000 mg of said FBPase inhibitor and from about 3 mg to about 250 mg of said sulfonylurea antidiabetic agent is administered to said mammal.

75. A pharmaceutical composition comprising a pharmaceutically effective amount of insulin or insulin analogue and a pharmaceutically effective amount of an FBPase inhibitor.

5 76. The pharmaceutical composition of claim 75 wherein said insulin or insulin analogue is selected from insulin, insulin lispro, insulin aspart, and insulin gargline.

77. A pharmaceutical composition comprising a pharmaceutically effective amount of a biguanide and a pharmaceutically effective amount of an FBPase inhibitor.

10 78. The pharmaceutical composition of claim 77 wherein said biguanide is selected from metformin, phenformin, and buformin.

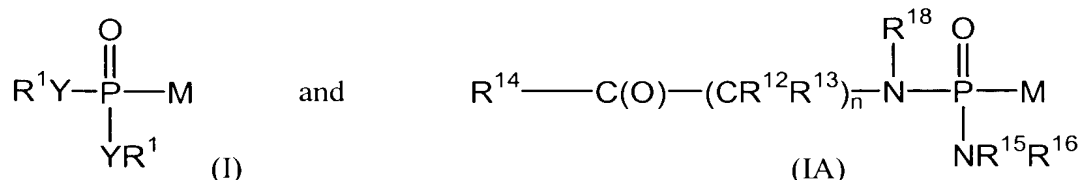
15 79. A pharmaceutical composition comprising a pharmaceutically effective amount of an alpha-glucosidase inhibitor and a pharmaceutically effective amount of an FBPase inhibitor.

80. The pharmaceutical composition of claim 79 wherein said alpha-glucosidase inhibitor is selected from acarbose, miglitol, and voglibose.

20 81. A pharmaceutical composition comprising a pharmaceutically effective amount of an FBPase inhibitor and a pharmaceutically effective amount of a hepatic glucose output inhibitor selected from glycogen phosphorylase inhibitors, glucose-6-phosphatase inhibitors, glucagon antagonists, amylin agonists, and fatty acid oxidation
25 inhibitors.

82. The pharmaceutical composition of claim 81 wherein said amylin agonist is pramlintide.

30 83. The pharmaceutical composition of claim 75, 77, or 79 wherein said FBPase inhibitor is a compound selected from formulae I and IA:



wherein *in vivo* or *in vitro* compounds of formulae I and IA are converted to M-PO_3^{2-} which inhibits FBPase and wherein

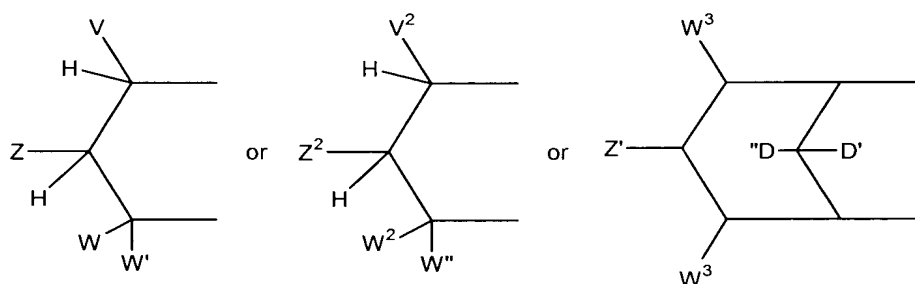
Y is independently selected from -O- and -NR⁶, with the provisos that:

5 when Y is -O-, the R¹ attached to -O- is independently selected from -H, alkyl, optionally substituted aryl, optionally substituted alicyclic where the cyclic moiety contains a carbonate or a thiocarbonate, optionally substituted -arylalkyl, -C(R²)₂OC(O)NR²₂, -NR²-C(O)-R³, -C(R²)₂-OC(O)R³, -C(R²)₂-O-C(O)OR³, -C(R²)₂OC(O)SR³, -alkyl-S-C(O)R³, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy;

when Y is -NR⁶-, the R¹ attached to -NR⁶- is independently selected from -H, -[C(R²)₂]_q-COOR³, -C(R⁴)₂COOR³, -[C(R²)₂]_q-C(O)SR, and -cycloalkylene-COOR³, where q is 1 or 2;

15 when only one Y is -O-, which -O- is not part of a cyclic group containing the other Y, the other Y is -N(R¹⁸)-(CR¹²R¹³)-C(O)-R¹⁴; and

when Y is independently selected from -O- and -NR⁶, together R¹ and R¹ are alkyl-S-S-alkyl- and form a cyclic group, or together, R¹ and R¹ form :



wherein

a) V is selected from the group of aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkynyl and 1-alkenyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V; or

5 Z is selected from the group of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2\text{aryl}$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$, $-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SCOR}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NHaryl}$, $-(\text{CH}_2)_p-\text{OR}^2$, and $-(\text{CH}_2)_p-\text{SR}^2$, where p is an integer 2 or 3; or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

15 W and W' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl and 1-alkynyl; or

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

20 b) V^2 , W^2 and W'' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

25 Z^2 is selected from the group of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{SR}^2$, $-\text{CH}_2\text{NHaryl}$, $-\text{CH}_2\text{aryl}$; or

30 together V^2 and Z^2 are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally containing 1 heteroatom, and substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or

aryloxy-carbonyloxy attached to a carbon atom that is three atoms from a Y attached to phosphorus;

c) Z' is selected from the group of -OH, -OC(O)R³, -OCO₂R³, and -OC(O)SR³;

D' is -H;

D'' is selected from the group of -H, alkyl, -OR², -OH, and -OC(O)R³;

each W³ is independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

with the proviso that:

a) V, Z, W, W' are not all -H and V², Z², W², W'' are not all -H ;

R² is selected from R³ and -H;

R³ is selected from alkyl, aryl, alicyclic, and aralkyl;

each R⁴ is independently selected from -H, and alkyl, or together R⁴ and R⁴ form a cyclic alkyl group;

R⁶ is selected from -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

n is an integer from 1 to 3;

R¹⁸ is independently selected from H, lower alkyl, aryl, aralkyl, or together with R¹² is connected via 1-4 carbon atoms to form a cyclic group;

each R¹² and R¹³ is independently selected from H, lower alkyl, lower aryl, lower aralkyl, all optionally substituted, or R¹² and R¹³ together are connected via 2-6 carbon atoms to form a cyclic group;

each R¹⁴ is independently selected from -OR¹⁷, -N(R¹⁷)₂, -NHR¹⁷, and -SR¹⁷;

R¹⁵ is selected from -H, lower alkyl, lower aryl, lower aralkyl, or together with R¹⁶ is connected via 2-6 atoms, optionally including 1 heteroatom selected from O, N, and S;

R^{16} is selected from $-(CR^{12}R^{13})_n-C(O)-R^{14}$, lower alkyl, lower aryl, lower aralkyl, or together with R^{15} is connected via 2-6 atoms, optionally including 1 heteroatom selected from O, N, and S;

each R^{17} is independently selected from lower alkyl, lower aryl, and lower aralkyl, or together R^{17} and R^{17} on N is connected via 2-6 atoms, optionally including 1 heteroatom selected from O, N, and S;

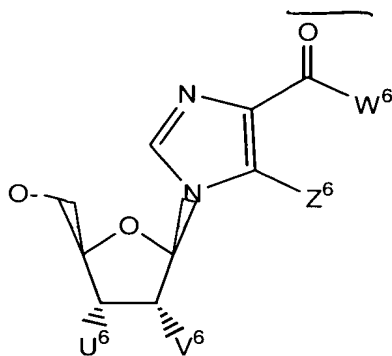
and pharmaceutically acceptable prodrugs and salts thereof.

84. The pharmaceutical composition of claim 83 wherein said composition comprises insulin or an insulin analogue selected from insulin, insulin lispro, insulin aspart, and insulin gargline.

85. The pharmaceutical composition of claim 83 wherein said composition comprises a biguanide selected from metformin, phenformin, and buformin.

86. The pharmaceutical composition of claim 83 wherein said composition comprises an alpha-glucosidase inhibitor selected from acarbose, miglitol, and voglibose.

87. The pharmaceutical composition of claim 83 wherein M is:



wherein

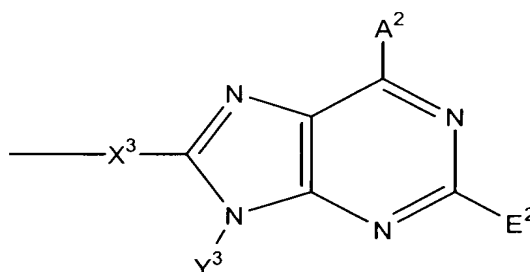
Z^6 is selected from alkyl or halogen;

U^6 and V^6 are independently selected from hydrogen, hydroxy, acyloxy or when taken together form a lower cyclic ring containing at least one oxygen;

W^6 is selected from amino and lower alkyl amino;

and pharmaceutically acceptable prodrugs and salts thereof.

88. The pharmaceutical composition of claim 83 wherein M is:



wherein:

A² is selected from -NR⁸₂, NHSO₂R³, -OR²⁵, -SR²⁵, halogen, lower alkyl, -CON(R⁴)₂, guanidine, amidine, -H, and perhaloalkyl;

E² is selected from -H, halogen, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and -NR⁷₂;

X³ is selected from -alkyl(hydroxy)-, -alkyl-, -alkynyl-, -aryl-, -carbonyl-alkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and -alkylaminocarbonylamino-, all optionally substituted; with the proviso that X³ is not substituted with -COOR², -SO₃H, or -PO₃R²₂;

Y³ is selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, -C(O)R³, -S(O)₂R³, -C(O)-R¹¹, -CONHR³, -NR²₂, and -OR³, all except H are optionally substituted;

each R⁴ is independently selected from -H and alkyl, or together R⁴ and R⁴ form a cyclic alkyl group;

R²⁵ is selected from lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

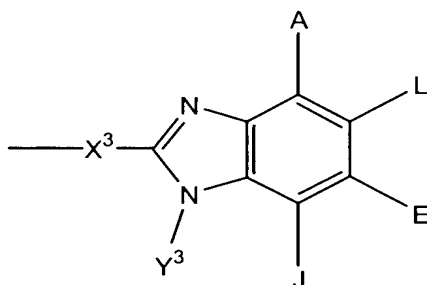
R⁷ is independently selected from -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and -C(O)R¹⁰;

R^8 is independently selected from -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^{10} is selected from -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl; and

R^{11} is selected from alkyl, aryl, $-NR^2_2$, and $-OR^2$, and pharmaceutically acceptable
5 prodrugs and salts thereof.

89. The pharmaceutical composition of claim 83 wherein M is:



wherein:

A, E, and L are selected from $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^{25}$, $-SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a
15 cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic
20 group including aryl, cyclic alkyl and heterocyclic alkyl;

X^3 is selected from -alkyl(hydroxy)-, -alkyl-, -alkynyl-, -aryl-, -carbonyl-alkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-,
25 -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and

-alkylaminocarbonylamino-, all optionally substituted; with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

Y^3 is selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are

5 optionally substituted;

R^4 is independently selected from -H and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^{25} is selected from lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^7 is independently selected from -H, lower alkyl, lower alicyclic, lower aralkyl,

10 lower aryl, and $-C(O)R^{10}$;

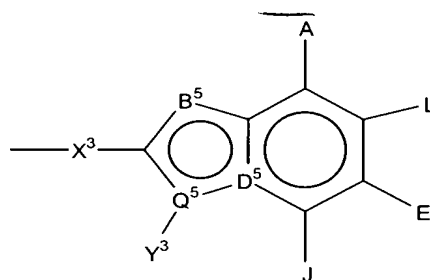
R^8 is independently selected from -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^{10} is selected from -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from alkyl, aryl, $-NR^2_2$, and $-OR^2$, and

15 pharmaceutically acceptable prodrugs and salts thereof.

90. The pharmaceutical composition of claim 87 wherein M is:



20 wherein:

B⁵ is selected from -NH-, -N= and -CH=;

D⁵ is selected from $\text{---}\overset{\textstyle |}{\text{C}}\text{=}$ and $\text{---}\overset{\textstyle |}{\text{N}}\text{---}$;

Q⁵ is selected from -C= and -N-;

with the provisos that:

when B⁵ is -NH-, Q⁵ is -C= and D⁵ is $\text{---}\overset{\textstyle |}{\text{C}}\text{=}$;

5 when B⁵ is -CH=, Q⁵ is -N- and D⁵ is $\text{---}\overset{\textstyle |}{\text{C}}\text{=}$; and

when B⁵ is -N=, D⁵ is $\text{---}\overset{\textstyle |}{\text{N}}\text{---}$ and Q⁵ is -C=;

A, E, and L are selected from -NR⁸₂, -NO₂, -H, -OR⁷, -SR⁷, -C(O)NR⁴₂, halo, -COR¹¹, -SO₂R³, guanidine, amidine, -NHSO₂R²⁵, -SO₂NR⁴₂, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C₁-C₅ alkyl, C₂-C₅ alkenyl, C₂-C₅ alkynyl, and
10 lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from -NR⁸₂, -NO₂, -H, -OR⁷, -SR⁷, -C(O)NR⁴₂, halo, -C(O)R¹¹, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl,
15 aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl;

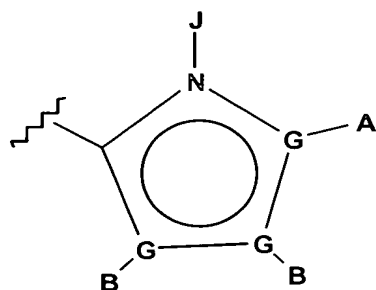
X³ is selected from -alkyl(hydroxy)-, -alkyl-, -alkynyl-, -aryl-, -carbonyl-alkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-,
20 -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and -alkylaminocarbonylamino-, all optionally substituted; with the proviso that X³ is not substituted with -COOR², -SO₃H, or -PO₃R²₂;

Y³ is selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, -C(O)R³, -S(O)₂R³, -C(O)-R¹¹, -CONHR³, -NR²₂, and -OR³, all except H are
25 optionally substituted;

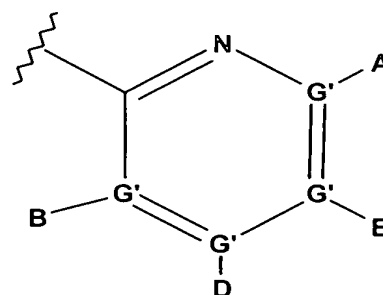
R⁴ is independently selected from -H and alkyl, or together R⁴ and R⁴ form a cyclic alkyl group;

R^{25} is selected from lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;
 R^7 is independently selected from -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;
 R^8 is independently selected from -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidentate alkyl;
 R^{10} is selected from -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;
 R^{11} is selected from alkyl, aryl, $-NR^2_2$ and $-OR^3$; and
pharmaceutically acceptable prodrugs and salts thereof.

91. The pharmaceutical composition of claim 83 wherein M is $-X-R^5$,
wherein R^5 is selected from:



and



wherein:

each G is independently selected from C, N, O, S, and Se, and wherein only one G is O, S, or Se, and at most one G is N;

each G' is independently selected from C and N and wherein no more than two G' groups are N;

A is selected from -H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, perhaloalkyl, haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, $-CN$, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, $-NHAc$, and null;

each B and D are independently selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, $-CN$, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, $-NO_2$, and null, all except -H, $-CN$, perhaloalkyl, $-NO_2$, and halo are optionally substituted;

E is selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, alkoxyalkyl, -C(O)OR³, -CONR⁴₂, -CN, -NR⁹₂, -NO₂, -OR³, -SR³, perhaloalkyl, halo, and null, all except -H, -CN, perhaloalkyl, and halo are optionally substituted;

J is selected from -H and null;

5 X is an optionally substituted linking group that links R⁵ to the phosphorus atom via 2-4 atoms, including 0-1 heteroatoms selected from N, O, and S, except that if X is urea or carbamate there are two heteroatoms, measured by the shortest path between R⁵ and the phosphorus atom, and wherein the atom attached to the phosphorus is a carbon atom, and wherein X is selected from -alkyl(hydroxy)-, -alkynyl-, -heteroaryl-,
10 -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-,
-alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-,
-alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and
-alkylaminocarbonylamino-, all optionally substituted; with the proviso that X is not substituted with -COOR², -SO₃H, or -PO₃R²₂;

15 R² is selected from R³ and -H;

R³ is selected from alkyl, aryl, alicyclic, and aralkyl;

each R⁴ is independently selected from -H, and alkyl, or together R⁴ and R⁴ form a cyclic alkyl group;

each R⁹ is independently selected from -H, alkyl, aralkyl, and alicyclic, or together

20 R⁹ and R⁹ form a cyclic alkyl group;

R¹¹ is selected from alkyl, aryl, -NR²₂, and -OR²;

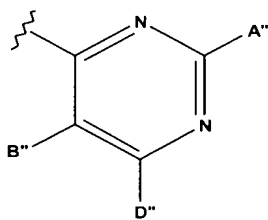
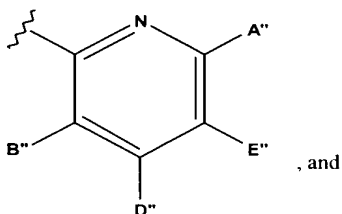
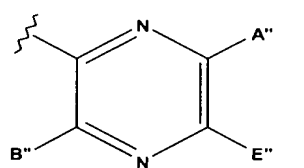
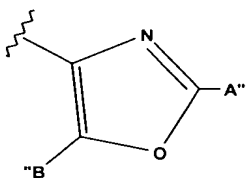
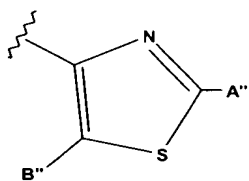
and with the proviso that:

- 1) when G' is N, then the respective A, B, D, or E is null;
- 2) at least one of A and B, or A, B, D, and E is not selected from -H or null;
- 25 3) when R⁵ is a six-membered ring, then X is not a two atom linker, an optionally substituted -alkyloxy-, or an optionally substituted -alkylthio-;
- 4) when G is N, then the respective A or B is not halogen or a group directly bonded to G via a heteroatom;
- 5) when X is not an -aryl- group, then R⁵ is not substituted with two or more
30 aryl groups;

and pharmaceutically acceptable prodrugs and salts thereof.

92. The pharmaceutical composition of claim 91 wherein R^5 is selected from pyrrolyl, imidazolyl, oxazolyl, thiazolyl, isothiazolyl, 1,2,4-thiadiazolyl, pyrazolyl, isoxazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, and 1,3-selenazolyl, all of which contain at least one substituent.

93. The pharmaceutical composition of claim 92 wherein R^5 is selected from:



wherein:

A'' is selected from -H, -NR⁴₂, -CONR⁴₂, -CO₂R³, halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perhaloalkyl, C₁-C₆ haloalkyl, aryl, -CH₂OH, -CH₂NR⁴₂, -CH₂CN, -CN, -C(S)NH₂, -OR³, -SR³, -N₃, -NHC(S)NR⁴₂, and -NHAc;

B'' and D'' are independently selected from -H, alkyl, alkenyl, alkynyl, aryl,
5 alicyclic, aralkyl, alkoxyalkyl, -C(O)R¹¹, -C(O)SR³, -SO₂R¹¹, -S(O)R³, -CN, -NR⁹₂, -OR³, -SR³, perhaloalkyl, and halo, all except -H, -CN, perhaloalkyl, and halo are optionally substituted;

E'' is selected from -H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₄-C₆ alicyclic, alkoxyalkyl, -C(O)OR³, -CONR⁴₂, -CN, -NR⁹₂, -OR³, -SR³, C₁-C₆ perhaloalkyl, and halo,
10 all except H, -CN, perhaloalkyl, and halo are optionally substituted; and

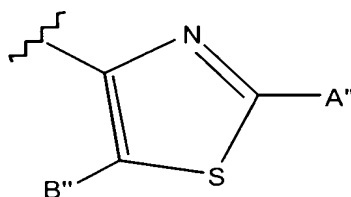
each R³ is independently selected from C₁ - C₆ alkyl, C₆ aryl, C₃ - C₆ heteroaryl, C₃ - C₈ alicyclic, C₂ - C₇ heteroalicyclic, C₇ - C₁₀ aralkyl, and C₄ - C₉ heteroaralkyl;

each R⁴ and R⁹ is independently selected from -H and C₁-C₂ alkyl;

X is selected from -heteroaryl-, -alkylcarbonylamino-, -alkylaminocarbonyl-, and
15 -alkoxycarbonyl-;

each R¹¹ is selected from -NR⁴₂, -OH, -OR³, C₁ - C₆ alkyl, C₆ aryl, and C₃ - C₆ heteroaryl.

94. The pharmaceutical composition of claim 93 wherein said FBPase inhibitor
20 is a compound of Formula IA and wherein R⁵ is:

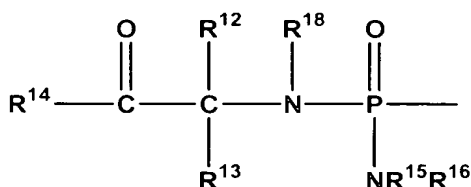


A'' is selected from -NH₂, -CONH₂, halo, -CH₃, -CF₃, -CH₂-halo, -CN, -OCH₃, -SCH₃, and -H;

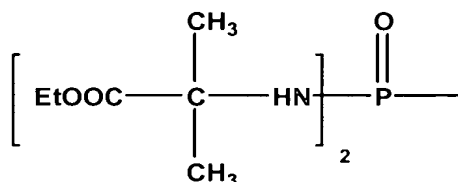
B'' is selected from -H, -C(O)R¹¹, -C(O)SR³, alkyl, aryl, alicyclic, halo, -CN, -SR³,
25 OR³ and -NR⁹₂;

X is selected from -heteroaryl-, -alkoxycarbonyl-, and -alkylaminocarbonyl-, all optionally substituted; and

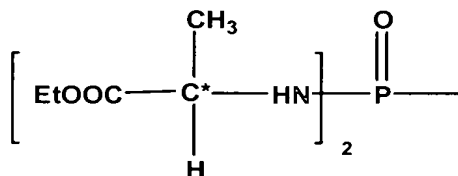
wherein



is selected from:



and



wherein:

C* has S stereochemistry;

R¹⁸ and R¹⁵ are each independently selected from H and methyl;

each R¹² and R¹³ is independently selected from -H, methyl, i-propyl, i-butyl, and benzyl, or, together, R¹² and R¹³ are connected via 2-5 carbon atoms to form a cycloalkyl group;

n is 1;

R¹⁴ is -OR¹⁷;

R¹⁶ is -(CR¹²R¹³)_n-C(O)-R¹⁴; and

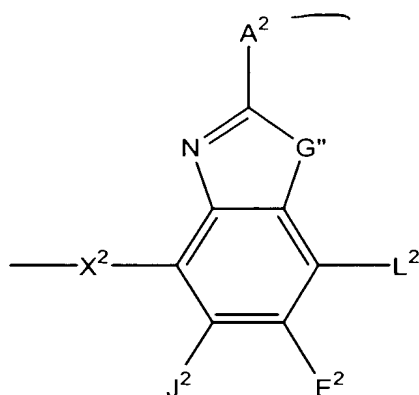
R¹⁷ is selected from methyl, ethyl, propyl, phenyl, and benzyl.

95. The pharmaceutical composition of claim 94 wherein said composition comprises insulin or an insulin analogue selected from insulin, insulin lispro, insulin aspart, and insulin gargline.

96. The pharmaceutical composition of claim 94 wherein said composition comprises a biguanide selected from metformin, phenformin, and buformin.

97. The pharmaceutical composition of claim 94 wherein said composition comprises an alpha-glucosidase inhibitor selected from acarbose, miglitol, and voglibose.

5 98. The pharmaceutical composition of claim 83 wherein M is:



wherein:

G'' is selected from -O- and -S-;

10 A², L², E², and J² are selected from -NR⁴₂, -NO₂, -H, -OR², -SR², -C(O)NR⁴₂, halo, -COR¹¹, -SO₂R³, guanidiny, amidiny, aryl, aralkyl, alkoxyalkyl, -SCN, -NHSO₂R⁹, -SO₂NR⁴₂, -CN, -S(O)R³, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together L² and E² or E² and J² form an annulated cyclic group;

15 X² is selected from -CR²₂-, -CF₂-, -CR²₂-O-, -CR²₂-S-, -C(O)-O-, -C(O)-S-, -C(S)-O-, and -CR²₂-NR¹⁹-, and wherein in the atom attached to the phosphorus is a carbon atom; with the proviso that X² is not substituted with -COOR², -SO₃H, or -PO₃R²₂;

R² is selected from R³ and -H;

20 R³ is selected from alkyl, aryl, alicyclic, and aralkyl;

each R⁴ is independently selected from -H, and alkyl, or together R⁴ and R⁴ form a cyclic alkyl group;

each R⁹ is independently selected from -H, alkyl, aralkyl, and alicyclic, or together R⁹ and R⁹ form a cyclic alkyl group;

R¹¹ is selected from alkyl, aryl, -NR²₂, and -OR²;

R¹⁹ is selected from lower alkyl, -H, and -COR²;

5 and pharmaceutically acceptable prodrugs and salts thereof.

99. A method of treating a mammal having diabetes comprising administering to said mammal:

10 a pharmaceutically effective amount of a component (a) comprising at least one of an insulin, an insulin analogue, a biguanide, a hepatic glucose output inhibitor, or an alpha-glucosidase inhibitor; and

a pharmaceutically effective amount of a component (b) comprising at least one FBPase inhibitor.

15 100. The method of claim 99 wherein said insulin or insulin analogue is selected from insulin, insulin lispro, insulin aspart, and insulin gargline.

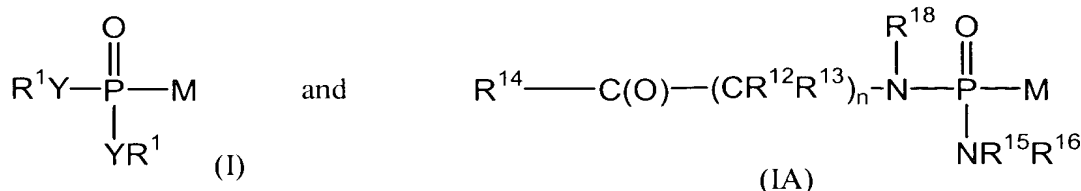
20 101. The method of claim 99 wherein said biguanide is selected from metformin, phenformin, and buformin.

102. The method of claim 99 wherein said hepatic glucose output inhibitor is selected from glycogen phosphorylase inhibitors, glucose-6-phosphatase inhibitors, glucagon antagonists, amylin agonists, and fatty acid oxidation inhibitors.

25 103. The method of claim 102 wherein said amylin agonist is pramlintide.

104. The method of claim 99 wherein said alpha-glucosidase is selected from acarbose, miglitol, and voglibose.

30 105. The method of claim 99 wherein said FBPase inhibitor is a compound selected from formulae I and IA:



wherein *in vivo* or *in vitro* compounds of formulae I and IA are converted to M-PO_3^{2-} which inhibits FBPase and wherein

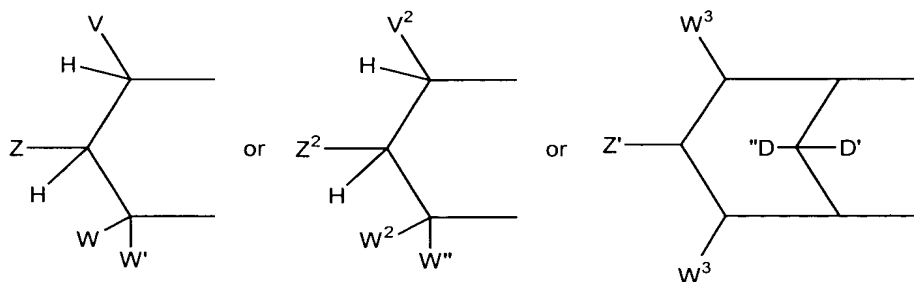
Y is independently selected from -O- and -NR⁶, with the provisos that:

when Y is -O-, the R¹ attached to -O- is independently selected from -H, alkyl, optionally substituted aryl, optionally substituted alicyclic where the cyclic moiety contains a carbonate or a thiocarbonate, optionally substituted -arylalkyl, -C(R²)₂OC(O)NR²₂, -NR²-C(O)-R³, -C(R²)₂-OC(O)R³, -C(R²)₂-O-C(O)OR³, -C(R²)₂OC(O)SR³, -alkyl-S-C(O)R³, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy;

when Y is -NR⁶-, the R¹ attached to -NR⁶- is independently selected from -H, -[C(R²)₂]_q-COOR³, -C(R⁴)₂COOR³, -[C(R²)₂]_q-C(O)SR, and -cycloalkylene-COOR³, where q is 1 or 2;

when only one Y is -O-, which -O- is not part of a cyclic group containing the other Y, the other Y is -N(R¹⁸)-(CR¹²R¹³)-C(O)-R¹⁴; and

when Y is independently selected from -O- and -NR⁶, together R¹ and R¹ are alkyl-S-S-alkyl- and form a cyclic group, or together, R¹ and R¹ form :



wherein

a) V is selected from the group of aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkynyl and 1-alkenyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V; or

5 Z is selected from the group of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2\text{aryl}$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$, $-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SCOR}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NHaryl}$, $-(\text{CH}_2)_p\text{-OR}^2$, and $-(\text{CH}_2)_p\text{-SR}^2$, where p is an integer 2 or 3; or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

15 W and W' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl and 1-alkynyl; or

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

b) V^2 , W^2 and W'' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

25 Z^2 is selected from the group of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{SR}^2$, $-\text{CH}_2\text{NHaryl}$, $-\text{CH}_2\text{aryl}$; or

30 together V^2 and Z^2 are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally containing 1 heteroatom, and substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or

aryloxycarbonyloxy attached to a carbon atom that is three atoms from a Y attached to phosphorus;

c) Z' is selected from the group of $-OH$, $-OC(O)R^3$, $-OCO_2R^3$, and $-OC(O)SR^3$;

D' is $-H$;

D'' is selected from the group of $-H$, alkyl, $-OR^2$, $-OH$, and $-OC(O)R^3$;

each W^3 is independently selected from the group of $-H$, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

with the proviso that:

a) V , Z , W , W' are not all $-H$ and V^2 , Z^2 , W^2 , W'' are not all $-H$;

R^2 is selected from R^3 and $-H$;

R^3 is selected from alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from $-H$, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^6 is selected from $-H$, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

n is an integer from 1 to 3;

R^{18} is independently selected from H , lower alkyl, aryl, aralkyl, or together with R^{12} is connected via 1-4 carbon atoms to form a cyclic group;

each R^{12} and R^{13} is independently selected from H , lower alkyl, lower aryl, lower aralkyl, all optionally substituted, or R^{12} and R^{13} together are connected via 2-6 carbon atoms to form a cyclic group;

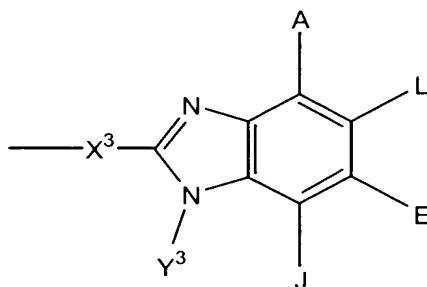
each R^{14} is independently selected from $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, and $-SR^{17}$;

R^{15} is selected from $-H$, lower alkyl, lower aryl, lower aralkyl, or together with R^{16} is connected via 2-6 atoms, optionally including 1 heteroatom selected from O , N , and S ;

R^{16} is selected from $-(CR^{12}R^{13})_n-C(O)-R^{14}$, lower alkyl, lower aryl, lower aralkyl, or together with R^{15} is connected via 2-6 atoms, optionally including 1 heteroatom selected from O , N , and S ;

each R^{17} is independently selected from lower alkyl, lower aryl, and lower aralkyl, or together R^{17} and R^{17} on N is connected via 2-6 atoms, optionally including 1 heteroatom selected from O, N, and S;

M comprises:



wherein:

A, E, and L are selected from $-NR^8_2$, $-NO_2$, $-H$, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^{25}$, $-SO_2NR^4_2$, $-CN$, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C_1 - C_5 alkyl, C_2 - C_5 alkenyl, C_2 - C_5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from $-NR^8_2$, $-NO_2$, $-H$, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, $-CN$, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl;

X^3 is selected from -alkyl(hydroxy)-, -alkyl-, -alkynyl-, -aryl-, -carbonyl-alkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and -alkylaminocarbonylamino-, all optionally substituted; with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

Y^3 is selected from $-H$, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted;

each R^4 is independently selected from -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^{25} is selected from lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

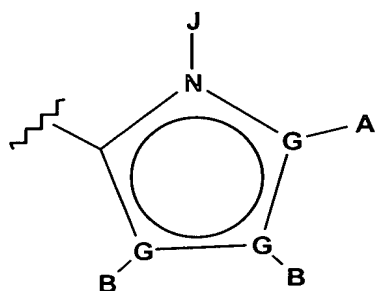
R^7 is independently selected from -H, lower alkyl, lower alicyclic, lower aralkyl,
5 lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

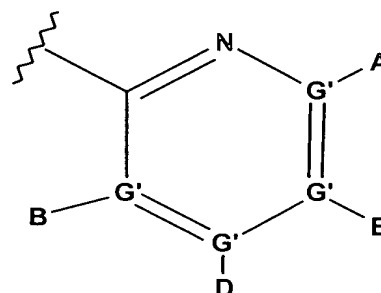
R^{10} is selected from -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from alkyl, aryl, $-NR^2_2$, and $-OR^2$, and

M is $-X-R^5$, wherein R^5 is selected from:



and



wherein:

each G is independently selected from C, N, O, S, and Se, and wherein only one G
15 is O, S, or Se, and at most one G is N;

each G' is independently selected from C and N and wherein no more than two G' groups are N;

A is selected from -H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, perhaloalkyl, haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, $-CN$,
20 $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, $-NHAc$, and null;

each B and D are independently selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, $-CN$, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, $-NO_2$, and null, all except -H, $-CN$, perhaloalkyl, $-NO_2$, and halo are optionally substituted;

E is selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, alkoxyalkyl, -C(O)OR³, -CONR⁴₂, -CN, -NR⁹₂, -NO₂, -OR³, -SR³, perhaloalkyl, halo, and null, all except -H, -CN, perhaloalkyl, and halo are optionally substituted;

J is selected from -H and null;

5 X is an optionally substituted linking group that links R⁵ to the phosphorus atom via 2-4 atoms, including 0-1 heteroatoms selected from N, O, and S, except that if X is urea or carbamate there are two heteroatoms, measured by the shortest path between R⁵ and the phosphorus atom, and wherein the atom attached to the phosphorus is a carbon atom, and wherein X is selected from -alkyl(hydroxy)-, -alkynyl-, -heteroaryl-,
10 -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonyl-amino-, -alkoxycarbonyl-, -carbonyloxy-alkyl-, -alkoxycarbonylamino-, and -alkylaminocarbonylamino-, all optionally substituted; with the proviso that X is not substituted with -COOR², -SO₃H, or -PO₃R²₂;

R² is selected from R³ and -H;

15 R³ is selected from alkyl, aryl, alicyclic, and aralkyl;

each R⁴ is independently selected from -H, and alkyl, or together R⁴ and R⁴ form a cyclic alkyl group;

each R⁹ is independently selected from -H, alkyl, aralkyl, and alicyclic, or together R⁹ and R⁹ form a cyclic alkyl group;

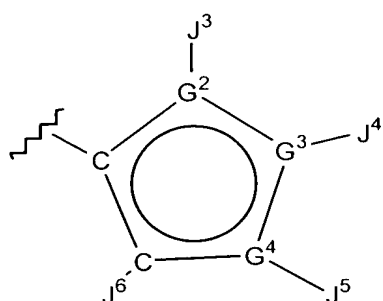
20 R¹¹ is selected from alkyl, aryl, -NR²₂, and -OR²;

and with the proviso that:

- 1) when G' is N, then the respective A, B, D, or E is null;
- 2) at least one of A and B, or A, B, D, and E is not selected from -H or null;
- 3) when R⁵ is a six-membered ring, then X is not a two atom linker, an
25 optionally substituted -alkyloxy-, or an optionally substituted -alkylthio-;
- 4) when G is N, then the respective A or B is not halogen or a group directly bonded to G via a heteroatom;
- 5) when X is not an -aryl- group, then R⁵ is not substituted with two or more
aryl groups.

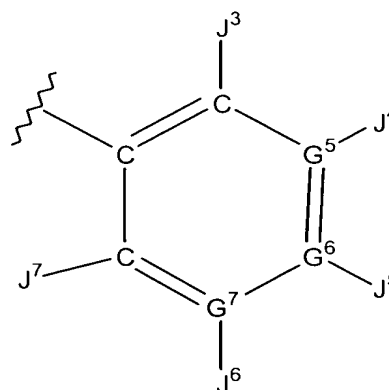
30 106. The pharmaceutical composition of claim 11 wherein M is -X⁴-R⁵⁵

wherein R^{55} is selected from:



VII-5

and



VII-6

wherein:

G^2 is selected from the group of C, O, and S;

G^3 and G^4 are independently selected from the group of C, N, O, and S;

wherein a) not more than one of G^2 , G^3 , and G^4 is O, or S; b) when G^2 is O or S, not more than one of G^3 and G^4 is N; c) at least one of G^2 , G^3 , and G^4 is C; and d) G^2 , G^3 , and G^4 are not all C;

G^5 , G^6 and G^7 are independently selected from the group of C and N, wherein no more than two of G^5 , G^6 and G^7 are N;

J^3 , J^4 , J^5 , J^6 , and J^7 are independently selected from the group of -H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, $-S(O)_2NR^4_2$, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, alkylenearyl, perhaloalkyl, haloalkyl, aryl, heteroaryl, alkylene-OH, $-C(O)R^{11}$, $-OR^{11}$, $-alkylene-NR^4_2$, $-alkylene-CN$, $-CN$, $-C(S)NR^4_2$, $-OR^2$, $-SR^2$, $-N_3$, $-NO_2$, $-NHC(S)NR^4_2$, and $-NR^{21}COR^2$;

X^4 is selected from:

i) a linking group having 2-4 atoms measured by the fewest number of atoms connecting the carbon of the aromatic ring and the phosphorus atom and is selected from the group of -furanyl-, -thienyl-, -pyridyl-, -oxazolyl-, -imidazolyl-, -phenyl-, -pyrimidinyl-, -pyrazinyl-, and -alkynyl-, all of which are optionally substituted; and

ii) a linking group having 3-4 atoms measured by the fewest number of atoms connecting the carbon of the aromatic ring and the phosphorus atom and is selected from the group of -alkylenecarbonylamino-,

-alkyleneaminocarbonyl-, -alkyleneoxycarbonyl-, -alkyleneoxy-, and
-alkyleneoxyalkylene-, all of which are optionally substituted;

R^{11} is selected from the group of alkyl, aryl, $-NR^2_2$, and $-OR^2$;

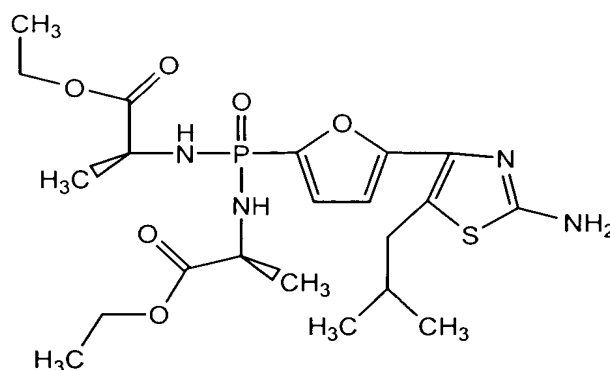
R^{20} is selected from the group of $-H$, lower R^3 , and $-C(O)-(lower\ R^3)$;

R^{21} is selected from $-H$ and lower R^3 ;

with the provisos that:

- 1) when G^5 , G^6 , or G^7 is N, then the respective J^4 , J^5 , or J^6 is null;
 - 2) when X^4 is substituted furanyl, then at least one of J^3 , J^4 , J^5 and J^6 is not $-H$ or null;
 - 3) when X^4 is not substituted furanyl, then at least two of J^3 , J^4 , J^5 and J^6 on formula VII-5 or J^3 , J^4 , J^5 , J^6 and J^7 on formula VII-6 are not $-H$ or null;
 - 4) when G^2 , G^3 , or G^4 is O or S, then the respective J^3 , J^4 or J^5 is null;
 - 5) when G^3 or G^4 is N, then the respective J^4 or J^5 is not halogen or a group directly bonded to G^3 or G^4 via a heteroatom;
 - 6) if both Y groups are $-NR^6-$, and R^1 and R^1 are not connected to form a cyclic phosphoramidate, then at least one R^1 is $-(CR^{12}R^{13})_n-C(O)-R^{14}$;
 - 7) when X^4 is -alkylenecarbonylamino- or -alkyleneaminocarbonyl-, then G^5 , G^6 , and G^7 are not all C;
 - 8) when X^4 is -alkeneoxyalkylene-, and G^5 , G^6 , and G^7 are all C, then neither J^4 nor J^6 can be substituted with an acylated amine;
 - 9) when R^{55} is substituted phenyl, then J^4 , J^5 and J^6 is not purinyl, purinylalkylene, deaza-purinyl, or deazapurinylalkylene;
 - 10) R^1 can be selected from the lower alkyl only when the other YR^1 is $-NR^{18}-C(R^{12}R^{13})_n-C(O)-R^{14}$;
 - 11) when R^{55} is substituted phenyl and X^4 is 1,2-ethynyl, then J^4 or J^6 is not a heterocyclic group;
 - 12) when X^4 is 1,2-ethynyl, then G^5 or G^7 cannot be N;
- and pharmaceutically acceptable prodrugs and salts thereof.

107. The pharmaceutical composition of claim 40, wherein said FB Pase inhibitor is



Compound J.

108. A method according to any one of claims 46 or 99, wherein said component (a) and said component (b) are administered within about one hour of each other.

109. A method according to claim 108, wherein said component (a) and said component (b) are administered within about 10 minutes of each other.

110. A method according to any one of claims 46 or 99, wherein one of said component (a) and said component (b) is administered first and the other of said component (a) and said component (b) is administered between 1 to 12 hours later.

111. A method according to any one of claims 46 or 99, wherein said mammal is a brittle diabetic.

112. A method according to any one of claims 46 or 99, wherein said mammal has NIDDM.

113. A method according to any one of claims 46 or 99, wherein said mammal has IDDM.

114. The pharmaceutical composition of claim 9 where said glucagon like peptide-1 (GLP-1) receptor agonist is NN-2211 or exendin.